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RESEARCH ARTICLE

Objective response to ethanol in essential tremor: results from a standardized ethanol challenge study

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Abstract

Background and Objectives: Ethanol has been reported to improve tremor severity in approximately two thirds of patients with essential tremor (ET), but the accuracy of that proportion is not certain and the mechanism of action is unknown. The goal of this study was to investigate alcohol response on tremor by applying an a priori objective response definition and subsequently to describe the responder rate to a standardized ethanol dose in a cohort of 85 ET patients. A secondary analysis evaluated other tremor and nontremor features, including demographics, tremor intensity, breath alcohol concentration, nontremor effects of alcohol, self-reported responder status to ethanol, and prior ethanol exposure. **Methods**: This was a prospective, open-label, single-dose challenge of oral ethanol during which motor and nonmotor measurements were obtained starting immediately prior to ethanol administration and subsequently every 20 min for 120 min. We defined tremor reduction as a 35% decline in power in the patient's tremor frequency recorded during spiral drawing 60 min after ethanol administration. **Results**: In total, 80% of patients were considered alcohol responsive using our objective definition. Responder status and change in the objective tremor metrics were significantly correlated with the change in breath alcohol concentration levels after ethanol administration, but no other relationships to nontremor metrics were found. **Discussion**: A high percentage of patients actually respond to acute ethanol. However, their self-reported response does not correlate well with their objective response. Objective response correlates with breath alcohol level but not with sedation, indicating a specific effect of ethanol on tremor.

Introduction

Essential tremor (ET) is one of the most common movement disorders worldwide, with an estimated prevalence of up to 5%.[1–3] Characterized by a bilateral 4–12 Hz tremor, ET occurs during posture and/or action and mainly affects the hands and forearms. Tremor may also be present in the head, voice, or lower limbs.[4] Many

patients with ET have trouble with activities of daily living, including eating, dressing, and handwriting. The severity of ET varies greatly between and also within individuals.[5]

Essential tremor is a centrally driven disorder originated by oscillatory firing in the brain that is propagated through the corticospinal tract to the limbs.[6] The cerebellum has been implicated in ET pathophysiology, as mild cerebellar dysfunction has been demonstrated clinically in patients with ET through such symptoms as gait disturbance, intention tremor, and dysmetria.[7–10] Neuropathological observations further suggest involvement of the cerebellum in ET's pathophysiology, as demonstrated by a loss of Purkinje cells, swelling of Purkinje cell bodies,[11] and abnormal synaptic connection formation of climbing fibers with Purkinje cells.[12–15]

Ethanol has been reported to improve tremor severity in two-thirds to three-fourths of patients with ET who report that they drink alcohol.[8,16,17] However, this metric relies on self-reported response data and may imply that ethanol response—or consequently also the lack thereof—in ET represents a specific phenotype within ET. In a study using an at-home spiral drawing test, 46% of patients exhibited a tremor that was sensitive to alcohol using an arbitrary definition of improvement of 3 points on the rating scale.[18] While the exact pathway of this effect is unknown, some hypotheses include ethanol's agonistic effect on $GABA_A$ receptors[19] and low threshold (T-type) calcium channels,[20] as well as the decrease in inferior olive neuronal firing rate in response to ethanol.[21–23] Elucidating the specific tremor-ameliorating central effects of ethanol, such as positive allosteric modulation of alpha6-subunit containing $GABA_A$ receptors of the cerebellar granule cells, can contribute to the identification and investigation of potential targets for the development of treatments in ET.[24]

In addition to improving tremor, ethanol affects multiple nonmotor domains which include alertness and mood changes. Specifically, ethanol causes both sedation and stimulation, although these effects follow different time courses after ethanol intake.[25] It is unknown whether the acute effects of ethanol on tremor are related to ethanol's primary nontremor effects in the central nervous system (CNS), or rather, if they reflect an independent effect of ethanol on tremor.

The goal of this study was to define a reasonable, a priori, objective definition of alcohol "responder," and subsequently to describe the responder rate to a standardized ethanol dose in ET patients who drink alcohol. For a secondary analysis, we evaluated other tremor and nontremor features including demographics, tremor intensity, nontremor response to alcohol, breath alcohol concentration, self-reported responder status to ethanol, and prior ethanol exposure, with the goal of delineating features that correlate with ethanol response.

Materials and Methods

This was a clinical trial (NCT01200966) registered with clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT01200966). The protocol was approved by the National Institutes of Health (NIH) Institutional Review Board on 8/20/2010 and approved by the registry on 09/11/2010. The first and last patients were enrolled on 12/17/2010 and 12/12/2014, respectively. All patients gave their written informed consent.

Patient recruitment and screening

Tremor severity was assessed clinically by both the performance and activities of daily living (ADL) portions of the TRG Essential Tremor Rating Assessment Scale (TETRAS).[26] The diagnosis of ET was evaluated and confirmed by a movement disorder specialist according to the 1998 Movement Disorder Society criteria.[27] Patients were required to have predominantly bilateral hand tremor and be over 21 years of age to participate. Patients with isolated head or voice tremor, or tremor affecting body parts other than the hands and forearms were excluded.

A full medical history and physical examination was performed to screen for any medical contraindications to ethanol administration. Patients with any other significant pathological finding in the neurological examination other than typical symptoms of ET were excluded. Other acute or chronic severe medical conditions were also assessed which would preclude the subject from participating (e.g., severe heart disease NYHA grade 3 or 4, renal failure, hepatic failure, lung disease, and uncontrolled hyperthyroidism).

A metabolic panel for liver function was administered, and patients with abnormal liver function parameters were excluded. Abnormal liver function parameters (AST, ALT, and GGT) were defined as those higher than the 1.5-fold upper limit of the normal range (as defined by the NIH Clinical Center Laboratory Medicine Department), setting the limit for AST at 51 U/L, 62 U/L for ALT, and 128 U/L for GGT. Patients with known flushing syndrome or allergic reactions to alcohol (determined by the Alcohol Flushing Questionnaire)[28] were also excluded.

Patients with active or past history of alcohol use disorder (≥9 on the Alcohol Use Disorders Identification Test (AUDIT)[29]) were excluded.

Patients taking medications known to interact with ethanol or affect brain excitability (e.g., hypnotic, antiepileptic, antipsychotic medication, stimulants, antihistamines,

and muscle relaxants), as well as female patients who were pregnant or lactating, were also excluded.

Patients who met all inclusion criteria were invited to return to NIH for the ethanol challenge portion of the study. Prior to this study visit, patients were required to refrain from alcohol and caffeine for 48 h, as well as abstain from any tremor medication for at least 5 plasma half-lives of the individual drug.

In total, 96 subjects enrolled in the study and completed the screening visit, from which 86 subjects were considered eligible. Ten subjects did not meet inclusion/exclusion criteria and were considered screening failures (reasons: elevated liver enzymes beyond cutoff: $n = 6$, diagnosis of essential tremor not confirmed: $n = 3$, uncontrolled medical comorbidity: $n = 1$). These 10 subjects were not entered into the active phase of the protocol. Of the 86 successfully screened subjects, one subject was withdrawn after the screening visit due to an unexpected serious adverse event that was determined to be unrelated to study procedures. The remaining 85 patients successfully completed the study.

Study intervention

This was a prospective, open-label, single-dose challenge of oral ethanol. A 95% ethanol solution was obtained from the NIH pharmacy and delivered orally at a total volume of 0.08 g/L of total body water (TBW), blended with a sugarless, caffeine-free soft-drink in a ratio of 1:3. TBW was calculated by an algorithm which controlled for patient height, weight, age, and gender to account for interindividual hepatic elimination rates.[28] Total ethanol dosage was calculated with the goal of reaching a peak breath alcohol concentration (BrAC) of 0.05 g/dL at 60 min postadministration, which is comparable to peak BrACs that would be achieved after rapid consumption of 2 to 3 standard drinks. Patients were asked to drink their dose within 5 min.

To control for effects of food on ethanol absorption and metabolism,[31] patients arrived in a fasting condition (last meal at least 8 h before) and received a standardized meal prior to the ethanol challenge.

Data collection measurements

Past drinking history was collected at baseline before ethanol administration through the Alcohol Timeline Followback (TLFB), a retrospective 90-day diary of alcohol consumption, and Self-Rating of the Effects (SRE) of alcohol scales.[32–34] The SRE is a 12-item self-report scale which asks an estimate of the number of drinks required for the patient to experience each of four conditions over different periods over their lives. For both scales, higher scores reflect higher previous drinking history. Prior to the ethanol challenge, participants were asked to self-report their prior history of tremor response to ethanol as either "yes," "no," or "unknown."

Throughout the ethanol challenge, we collected a series of metrics (detailed below), starting immediately prior to ethanol administration (baseline) and subsequently every 20 min up to 120 min, unless otherwise indicated.

Tremor severity was assessed clinically by the TETRAS performance and quantitatively by a previously validated digital spiral collection software (Neuroglyphics, www.neuroglyphics.org).[35] For spiral drawing, subjects were asked to sit upright with a tablet PC placed on a table in front of them at about mid-thoracic level. The right- and left-hand spirals were drawn clockwise and counterclockwise, respectively, with only the tip of the pen touching the surface and the drawing hand lifted up. Spectral analysis was performed off-line to calculate the spectral peak —a value that represents the power or strength of the tremor.[35] To account for baseline variability and practice effects, we used a mean of two measurements 15 min apart before ethanol administration as baseline for the spiral analysis. These metrics were also recorded at the time of discharge.

BrAC was obtained via breathalyzer readings at baseline and throughout the ethanol challenge, as well as at the time of discharge.

To measure the nonmotor effects of ethanol, additional validated scales were administered. The Biphasic Alcohol Effects Scale (BAES) is a self-report questionnaire shown to reliably measure stimulant and sedative effects of alcohol.[36] Patients assessed their experience with 14 subjective states, 7 associated with stimulation (elated, energized, excited, stimulated, talkative, up, and vigorous) and 7 with sedation (difficulty concentration, down, heavy head, inactive, sedated, slow thoughts, and sluggish) on a scale from 0 to 10, with higher numbers corresponding to greater symptom intensity. The sedation (BSED) and stimulation (BSTIM) scores were each summed separately.

Items from the Drug Effects Questionnaire (DEQ) were adapted to measure general drug effects,[37] specifically the effects of ethanol. Our adapted DEQ asked patients to respond to the following questions: "Do you feel any drug effects?", "Do you like the effects you are feeling now?", "Would you like more of what you received, right now?", "Do you feel high?", and "Do you feel intoxicated?". Responses were rated using a visual analog scale (VAS) between the extremes "0-Not at all" and "100-A lot."

The 8-item Alcohol Urge Questionnaire (AUQ) asked patients to describe their current urge to drink alcohol.[38] Patients responded to statements including "I crave a drink right now" and "All I want to do now is have a

drink" by marking their level of agreement along a VAS between "strongly disagree" and "strongly agree" as the extremes. In addition to baseline and during the ethanol challenge, the BAES, DEQ, and AUQ were also recorded at time point 0, immediately after the drink was consumed.

Data processing

Motor data (TETRAS performance, digital spirals) were normalized using the ratio of 60 min to baseline. Thus, a score of 1 indicates no change from baseline and values toward 0 represent a decrease from baseline. Nonmotor data (BAES, DEQ, AUQ) were normalized as a raw change from baseline.

To account for any nonalcohol-related practice effect of spiral drawing, we set an operational cutoff for being considered a responder at a minimum improvement of 35% (as measured by tremor power) as compared to the baseline measurements. This was intended to exceed diurnal variations in tremor,[39] which defined a coefficient of variation of 0.32 when objectively quantifying tremor amplitude over a period of 6 h. Therefore, a reduction of 35% or greater from baseline would be more than one standard deviation from the group mean. We considered this to be a pragmatic threshold for a putative "response" to the intervention. This evaluation of improvement occurred at 60 min after ethanol administration, a timepoint at which alcohol has been previously shown to have its maximum effect in reducing tremor severity after a single-dose oral challenge.[30,40]

Outcomes

The primary outcome was to evaluate the rate of alcohol responsiveness, that is, the percentage of our study population that showed a response to ethanol given the above definition, which we hypothesized to be 65% of our patient sample. We considered this to be a conservative assumption that lies within the published range of 60–74%.[8,16,17]

In addition to this primary goal, we also conducted additional exploratory outcomes. These included the evaluation of (1) TETRAS performance scores 60 min after ethanol administration; (2) time course of changes in spiral and TETRAS metrics after ethanol administration; (3) patient's self-reported and objective (spiral drawing) response to ethanol; (4) changes in nonmotor questionnaire data and BrAC at 60 min and generally over time after ethanol administration; (5) relationships between motor, nonmotor, and BrAC data over the course of the ethanol challenge; and (6) relationships between motor and nonmotor data collected during the ethanol challenge and data collected during screening and baseline, including demographics and drinking history.

Statistics

Our hypothesis regarding the expected rate of ethanol-responders was set to 65% of the study population. Assuming under a null hypothesis, that response is driven by chance, and not by ethanol (responder rate 50%), using two-sided χ^2 test with a power of 80% and alpha-level of 0.05, 85 subjects were needed to accept or reject our hypothesis.

The significance level was set at $P < 0.05$, although a majority of the analyses were exploratory and should be interpreted as such. We used Spearman's rho for correlation analysis, Wilcoxon signed-rank test for one-group testing, and Wilcoxon rank sum test for two-group testing. All tests were nonparametric in nature to maintain robustness for distributional irregularities in our metrics of interest. One-group testing investigated changes from baseline to 60 min, and two-group testing investigated changes between groups in normalized scores at 60 min. A correlation matrix of normalized data at 60 min is shown across key motor and questionnaire endpoints. In the reported analyses below, data are shown as median (interquartile range) unless otherwise noted.

Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.

Results

Baseline characteristics

We recruited 85 patients with ET (47 male, 80 right-handed), with median age of 66 (56–72) years, median age of tremor onset of 21 (14–47) years, and median tremor duration of 32 (17–49) years. The Essential Tremor Rating Assessment Scale (TETRAS) total performance and ADL scores from the screening visit were 24 (21–27) and 26 (23–30), respectively. Out of the 85 total patients, 66 self-reported a response in their tremor to alcohol, 6 reported no response, and 13 indicated that they were unsure. A summary of all screening visit data can be found in Table 1.

Responder rate for study population

Spiral data collected 60 min after ethanol administration revealed that 68 of 85 patients showed a 35% or greater decrease in power at the tremor frequency ($P < 0.001$). This meant that 80% of our participants were considered responders.

Table 1. Demographics and baseline characteristics of the patients enrolled in the study (n = 85), organized by responder group as defined by the change in the dominant-hand spiral score 60 min postethanol administration relative to baseline.

	Total group (n = 85)	Objective responder (n = 68)	Objective nonresponder (n = 17)	Responder versus nonresponder (P-value)
Demographics and tremor history				
Gender (M/F)	47/38	39/29	8/9	0.59
Handedness (r/L)	80/5	64/4	16/1	1
Age at consent (median [IQR])	66 (56–72)	66.5 (57.8–72)	64 (54–70)	0.29
Age at tremor onset (median [IQR])	21 (14–47)	20 (12–47.2)	30 (18–41)	0.49
Tremor duration (median [IQR])	32 (17–49)	36 (17.8–50.2)	28 (17–45)	0.38
Height (centimeters, median [IQR])	173 (165–178)	173 (167–179)	173 (165–178)	0.63
Weight (kg, median [IQR])	79.7 (68.4–92)	81.2 (70.8–96.8)	70.7 (65.5–82.5)	0.09
Patient's self-reported response to alcohol				
Reports no response to alcohol (n, %)	6 (7.1%)	5 (7.4%)	1 (5.9%)	0.21
Reports uncertainty of response to alcohol (n, %)	13 (15.3%)	8 (11.8%)	5 (29.4)	
Reports a response to alcohol (n, %)	66 (77.6%)	55 (80.9)	11 (64.7)	
The Essential Tremor Rating Assessment Scale (TETRAS)				
Baseline TETRAS performance score (median [IQR])	24 (21–27)	24.5 (21–29.1)	22.5 (19–25)	0.11
Baseline TETRAS Activities of daily living score (median [IQR])	26 (23–30)	26 (23–30)	25 (23–29)	0.35
Alcohol Use Disorders Identification Test (AUDIT)				
AUDIT score (median [IQR])	3 (2–4)	4 (2.8–5)	2 (1–3)	0.007
The Alcohol Timeline Followback (TLFB)				
TLFB: number of drinks (median [IQR])	40 (13–85)	49 (17.8–97.5)	18 (6–31)	0.012
TLFB: number of drinking days (median [IQR])	24 (8–64)	26.5 (10–75)	18 (5–24)	0.018
TLFB: number of drinks per day (median [IQR])	1.4 (1.05–2.01)	1.49 (1.1–2.1)	1.7 (1–2)	0.21
Self-Rating of the Effects of Alcohol (SRE)				
SRE—total (median [IQR])	2.8 (2–4)	2 (1.7–3)	1.5 (1–2.5)	0.06
SRE—first five (median [IQR])	2 (1.5–3)	3 (2–3.7)	2.5 ± 2.3	0.11
SRE—recent (median [IQR])	2.7 (2–3.7)	3.6 (2.7–5)	3.1 (2–5)	0.048
SRE—heaviest (median [IQR])	3.5 (2.7–5)	3 (2.3–4.1)	2.1 (1.5–2.8)	0.46

P-values are reported from Fisher's exact test or Wilcoxon rank sum test, as appropriate, for comparison between responder groups.

We did not find a significant difference in demographic data when comparing the responder and nonresponder groups (Table 1). Responders (29 female; 39 male) had a median age of 66.5 (57.8–72) at time of consent, a median age of tremor onset of 20 (12–47.2), and median tremor duration of 36 (17.8–50.2) years. Nonresponders (9 female; 8 male) had a median age of 64 (54–70) at time of consent, median age of tremor onset of 30 (18–41), and median tremor duration of 28 (17–45) years.

Normalized dominant hand spiral score for responders versus nonresponder groups

At 60 min postethanol administration, the responders had a median normalized change in tremor power of their dominant spiral data of 0.39 (0.26–0.50) for the dominant side (Fig. 1A, B). The median normalized change for the nonresponders was 0.82 (0.75–0.94) (Fig. 1A, B); the difference between these groups was significant ($P < 0.001$). Similar changes were observed in the nondominant hand for both groups (Table 2).

In addition to evaluating changes in tremor power, we also reviewed whether there were any corresponding changes to tremor frequency at 60 min postethanol administration. However, we found that tremor frequency remained similar throughout the time course of the experiment (Wilcoxon signed-rank test $P = 0.38$).

At 60 min postethanol administration, median Breath alcohol concentration (BrAC) values were 0.050 (0.044–0.057) and 0.046 (0.043–0.053) g/dL for the responders and nonresponders, respectively (Fig. 1C, D). These within-group changes were statistically significant for both groups when compared to baseline. While the BrAC value for the responder group was slightly higher at 60 min, there was not a significant difference between groups (Wilcoxon rank sum test $P = 0.24$).

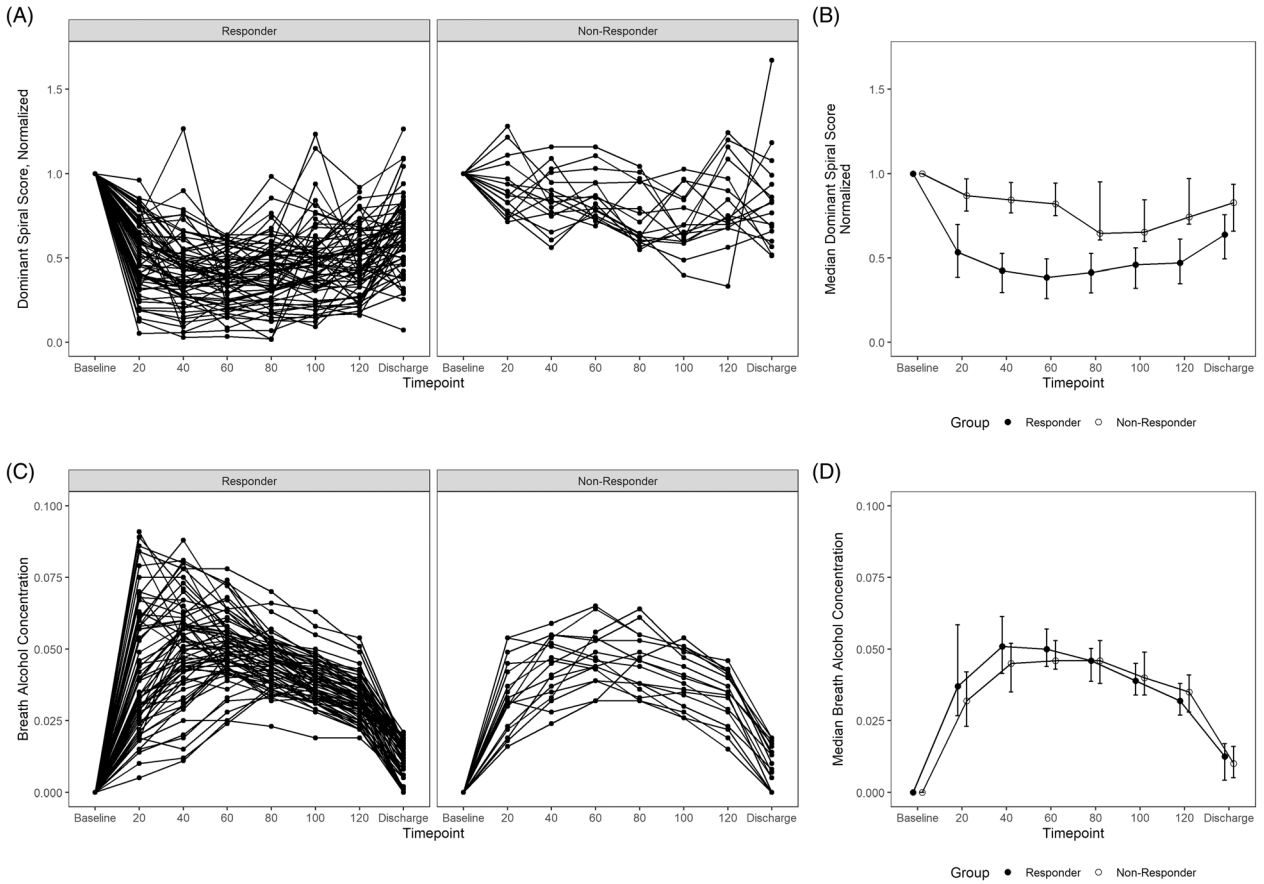

Figure 1. (A) Normalized dominant-hand spiral scores for all time points postethanol administration for responders and nonresponders. Each line represents one patient. (B) Median normalized dominant-hand spiral scores for all time points for responders and nonresponders, with accompanying interquartile ranges. (C) breath alcohol concentration (BrAC) levels for all time points postethanol administration for responders and nonresponders. Each line represents one patient. (D) Median BrAC levels for all time points for responders and nonresponders, with accompanying interquartile ranges.

Post hoc review of the spiral responder data revealed that the largest normalized decrease occurred at different times for different patients. While the largest number of responders (16) had the largest decrease when evaluated 60 min after ethanol administration, 4 patients had their largest decrease after 20 min, 12 after 40 min, 13 after 80 min, 12 after 100 min, 7 after 120 min, and 4 at the time of discharge (Fig. 2A). In addition, all but 4 of the nonresponders also showed a 35% or greater decrease in normalized spiral score, although not at the 60-min time point.

Similarly, the time of peak BrAC values differed among individual patients and were slightly higher relative to the 60 min time point, measuring at 0.057 (0.046–0.068) and 0.052 (0.046–0.055) g/dL for the responders and nonresponders, respectively. While the largest number of patients (27) had a peak BrAC 60 min after ethanol administration, 14 patients had their peak after 20 min, 26 after 40 min, 14 after 80 min, and 4 after 100 min (Fig. 2B).

Given the unique timings of peak change in BrAC and normalized spiral score, we evaluated these data at all time points to explore any potential relationship. When dividing the responders into groups based on when they achieved peak BrAC, we found that BrAC values peaked earlier in this group, and within individual patients there was a trend for a larger and more sustained decrease in normalized spiral score if the BrAC value increased more quickly after ethanol administration (Fig. 3).

Additional motor metrics

Using the same definition to group responders and nonresponders (change in normalized spiral score 60 min postethanol administration), we assessed differences in the other metrics collected between baseline and 60 min

Table 2. Median changes in motor and nonmotor scores for responder and nonresponder groups comparing scores at baseline (pre-ethanol administration) to those recorded 60 min after ethanol administration.

	Objective responder (n = 68)		Objective nonresponder (n = 17)		
	Median (IQR)	Baseline versus 60 min (P-value)	Median (IQR)	Baseline versus 60 min (P-value)	Responder versus nonresponder (P-value)
Data normalized at 60 min to baseline					
Spiral dominant	0.39 (0.26 to 0.50)	<0.001	0.82 (0.75 to 0.94)	0.001	<0.001
Spiral nondominant	0.50 (0.32 to 0.64)	<0.001	0.61 (0.48 to 0.94)	0.009	0.049
Baseline TETRAS performance score	0.72 (0.63 to 0.80)	<0.001	0.76 (0.70 to 0.79)	<0.001	0.4
Raw value (g/dL)					
Breath alcohol concentration	0.050 (0.044 to 0.057)	<0.001	0.046 (0.043 to 0.053)	<0.001	0.24
Data indicate a raw change from baseline to 60 min					
Stimulation – subset of the Biphasic Alcohol Effects Questionnaire (BSTIM, BAES)	5 (0 to 12)	<0.001	5 (−1 to 11)	0.06	0.83
Sedation – subset of the Biphasic Alcohol Effects Questionnaire (BSED, BAES)	-3 (−11.2 to 3)	0.03	−10 (−16 to 0)	0.02	0.09
Drug Effects Questionnaire (DEQ)	120 (63.8 to 183)	<0.001	149 (52.4 to 242)	<0.001	0.49
Alcohol Urge Questionnaire (AUQ)	0 (−1.0 to 16.1)	0.17	0 (−10.5 to 0)	0.41	0.17

P-values are reported from Wilcoxon signed-rank test for within-group change and from Wilcoxon rank sum test for between-group change.

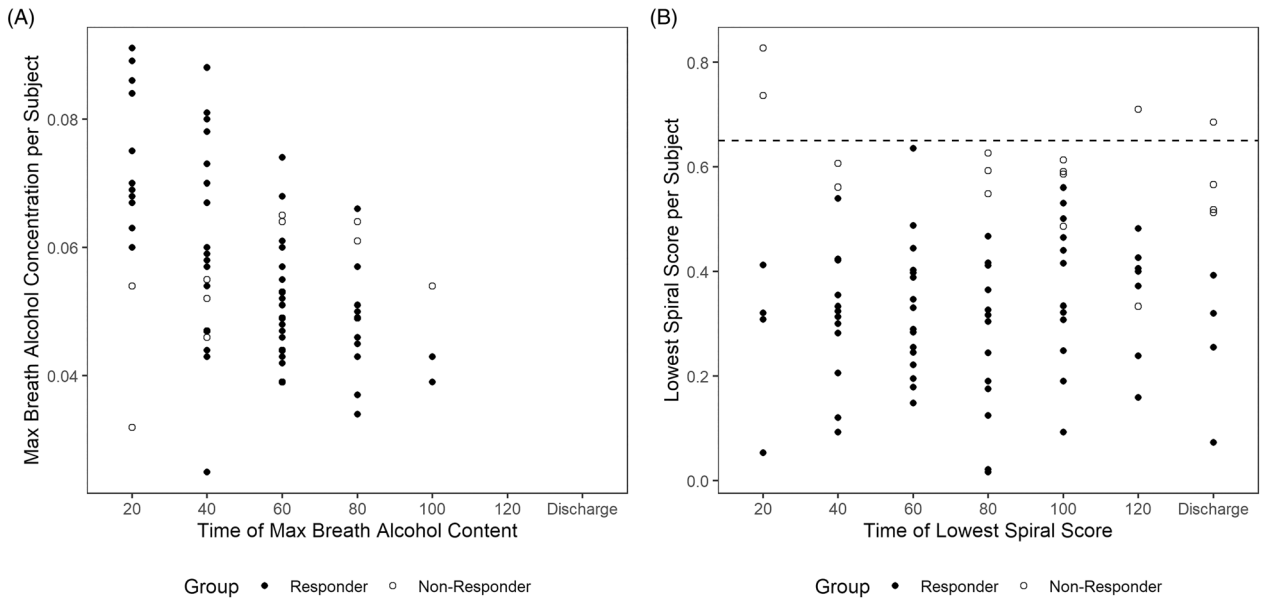

Figure 2. (A) Plot depicting the timing of the lowest normalized dominant-hand spiral score for responders (black dots) and nonresponders (red dots). Each dot represents one patient, and a score below 1 indicates a reduction in spiral score relative to baseline. The horizontal dotted line indicates the 35% reduction defined by our a priori definition for tremor reduction. (B) Plot depicting the timing of the breath alcohol concentration (BrAC) levels for responders (black dots) and nonresponders (red dots). Each dot represents one patient.

postethanol administration. We found that the change in median normalized TETRAS performance score at 60 min postadministration was significant for the responders (0.72 [0.63–0.80]) and the nonresponders (0.76 [0.70–0.79]). However, there was not a significant difference between groups (Table 2).

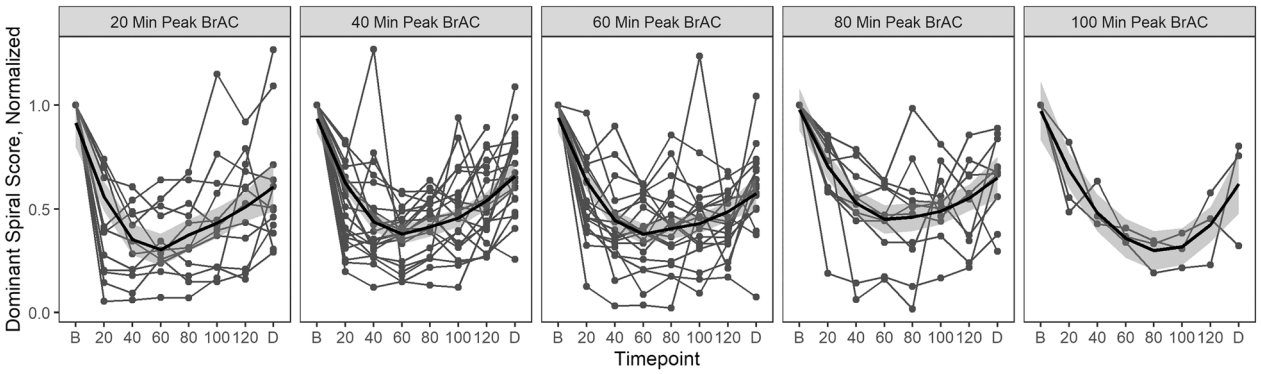

Figure 3. Normalized dominant-hand spiral scores for all time points postethanol administration for responders. Each line represents one patient. Patients are sorted into time blocks that represent their time of peak breath alcohol concentration (BrAC) levels, in minutes. The blue line represents a LOESS (locally-weighted smoothing) curve, with span of 1, based on all patients reported in each subplot.

The median TETRAS performance and ADL scores collected at baseline were not significantly different between groups, with values of 24.5 (21–29.1) and 26 (23–30) for the responders and 22.5 (19–25) and 25 (23–29) for the nonresponders, respectively (Table 1).

Additional nonmotor metrics

The median Alcohol Use Disorders Identification Test (AUDIT) score was significantly higher for responders (4 [2.8–5]) relative to the nonresponders 2 (1–3). The median Self-Rating of the Effects of alcohol scales (SRE) score for recent drinking history was significantly higher for responders (3.6 [2.7–5]) relative to the nonresponders (3.1 [2–5]) (Table 1).

For the Alcohol Timeline Followback (TLFB), responders reported a significantly higher median total number of 49 (17.8–97.5) drinks, with 26.5 (10–75) drinking days in the past 90 days. Nonresponders reported a median 18 (6–31) drinks, with 18 (5–24) drinking days in the past 90 days (Table 1).

During ethanol administration, there were significant differences for the sedation (BSED) and stimulation (BSTIM) portion of the Biphasic Alcohol Effects Scale (BAES). There was a significant difference in BSED change score (baseline to 60 min postadministration) for both responders (−3 [−11.2 to 3]) and nonresponders (−10 [−16 to 0]; Fig. 4). There was also a significant difference in BSTIM change score for the responders (5 [0 to 12]), but not for the nonresponders (5 [−1 to 11]). For the Drug Effects Questionnaire (DEQ), there was a significant difference in change score for both responders (120 [63.8–183]) and nonresponders (149 [52.4–242]). Despite these within-group changes, there were no significant differences between responders and nonresponders for the BSTIM, BSED, DEQ, or Alcohol Urge Questionnaire (AUQ; Table 2).

Self-reported versus objective response to the ethanol challenge

Overall, we found that self-reported response to ethanol did not seem to correlate well with objective responses. In the responder group, 81% (55/68) of patients correctly identified themselves as responders, which suggests the classifications are highly sensitive. However, a high proportion of nonresponders also classified themselves as responders (65%, 11/17), which was not significantly different from the responder group ($P = 0.27$). Only 1 out of 17 nonresponders correctly identified as a nonresponder (6%; specificity; Table 3).

Relationships between all metrics

We looked at correlations of all data at the 60-min time point and found significant negative correlations between dominant spirals and both BrAC (Spearman's rho (ρ) = −0.22; $P = 0.04$) and BSED ($\rho = -0.24$; $P = 0.03$; Table 4; Fig. 5). In addition, we found significant positive correlations between the DEQ and both the BSTIM ($\rho = 0.32$; $P = 0.003$) and AUQ ($\rho = 0.22$; $P = 0.04$); Table 4). Of note, there was a significant negative correlation between peak BrAC and normalized spirography at 60 min ($\rho = -0.22$; $P = 0.04$). Spiral amplitude at 60 min was negatively correlated with the total number of drinks reported in the TLFB ($\rho = -0.22$, $P = 0.04$) and with total SRE reported ($\rho = -0.24$, $P = 0.03$).

Discussion

We studied the effect of ethanol on 85 patients with ET through an oral-ethanol challenge and demonstrated that ethanol was associated with a reduction in tremor severity in 80% of our patients, using a pragmatic definition of response. Our data show that across the study

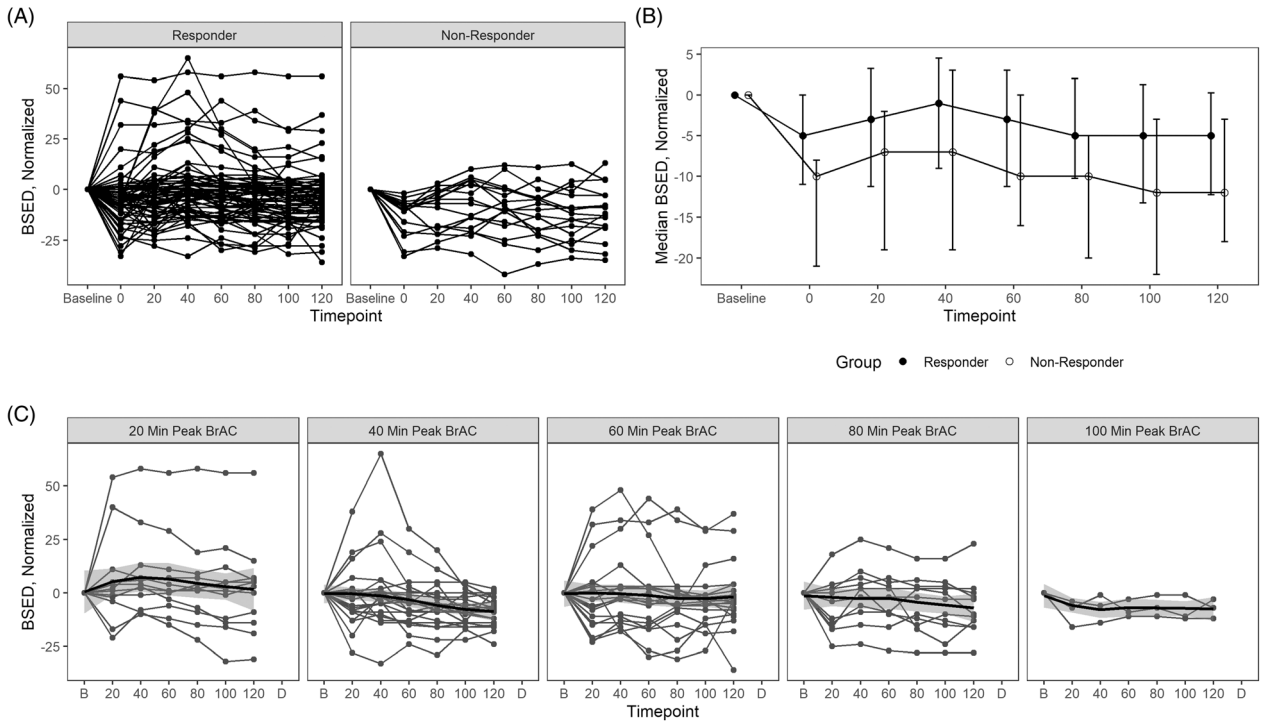

Figure 4. (A) Normalized BSED scores for all time points postethanol administration for responders and nonresponders. Each line represents one patient. (B) Median normalized BSED scores for all time points for responders and nonresponders, with accompanying interquartile ranges. (C) Normalized BSED scores for all time points postethanol administration for responders. Each line represents one patient. Patients are sorted into time blocks that represent their time of peak breath alcohol concentration (BrAC) levels, in minutes. The blue line represents a LOESS (locally-weighted smoothing) curve, with span of 1, based on all patients reported in each subplot. BSED: Sedation scores from the Biphasic Alcohol Effects Scale.

Table 3. Specific counts regarding whether a participant's self-reported response to whether or not their tremor is responsive to alcohol matches whether they were objectively responsive to alcohol.

	Objective classification	
	Nonresponder	Responder
Subjective classification		
No (nonresponder)	1	5
Yes (responder)	11	55
Unknown	5	8

participants, which included self-reported responders and nonresponders to ethanol, there was no evidence of a clear distinction between groups of responders or nonresponders following the objective ethanol challenge. Moreover, the correlation between BrAC and reduction in tremor amplitude suggests a dose–response relationship between ethanol and tremor reduction. This suggests that the level of ethanol response is driven, at least in part, by the ethanol exposure. Our data therefore speak to the notion that tremor-responsitivity to alcohol may be an inherent characteristic in patients with ET.

Interestingly, self-reported status of ethanol response did not predict objective response. While the screening for self-reported classification as responder or nonresponder (including those whose response is "unknown") shows acceptable sensitivity, the specificity has been shown to be low in our sample of ET patients. While our study design does not allow any conclusion around the specificity or sensitivity of self-reported ethanol response as diagnostic criterion in ET, given that ethanol responsivity is a key element of tremor history, our data demonstrate that an affirmative answer may be reasonably predictive of ethanol response, but a negative or unknown response answer is not sufficiently predictive, and a tremor response cannot be reliably ruled out based on a historical question. This finding is in line with a prior study by Hopfner et al., which found no relation between history of responsivity to alcohol and response on a spiral tremor severity rating scale following an at-home alcohol challenge.[18] This finding also has implications for subject selection in relevant clinical trials.

The rate of alcohol responders estimated from our study is higher relative to that reported in the study by Hopfner et al., which can likely be explained by different

Table 4. Numerical correlation matrix representing the relationship between motor and nonmotor data collected during the ethanol challenge.

	BrAC	Spiral (dominant)	Spiral (nondominant	TETRAS (total)	AUQ	DEQ	BSED	BSTIM
BrAC								
Spiral (dominant)	−0.22 (0.041)							
Spiral (nondominant	−0.18 (0.100)	0.38 (0.000)						
TETRAS (total)	−0.18 (0.093)	0.17 (0.119)	0.17 (0.116)					
AUQ	−0.04 (0.738)	−0.03 (0.786)	−0.06 (0.598)	0.07 (0.516)				
DEQ	−0.12 (0.285)	0.11 (0.301)	−0.02 (0.883)	0.01 (0.962)	0.22 (0.041)			
BSED	0.1. (0.366)	−0.24 (0.026)	−0.14 (0.187)	−0.02 (0.834)	0 (0.986)	0.13 (0.254)		
BSTIM	−0.2 (0.064)	0.04 (0.710)	−0.06 (0.596)	−0.15 (0.177)	0.06 (0.555)	0.32 (0.003)	0.32 (0.075)	

Values represent correlation value, with the *P*-value in parenthesis. TETRAS, The Essential Tremor Rating Scale; BrAC, breath alcohol concentration; AUQ, Alcohol Urge Questionnaire; BSED, Sedation scores from the Biphasic Alcohol Effects Scale; BSTIM, Stimulation scores from the Biphasic Alcohol Effects Scale.

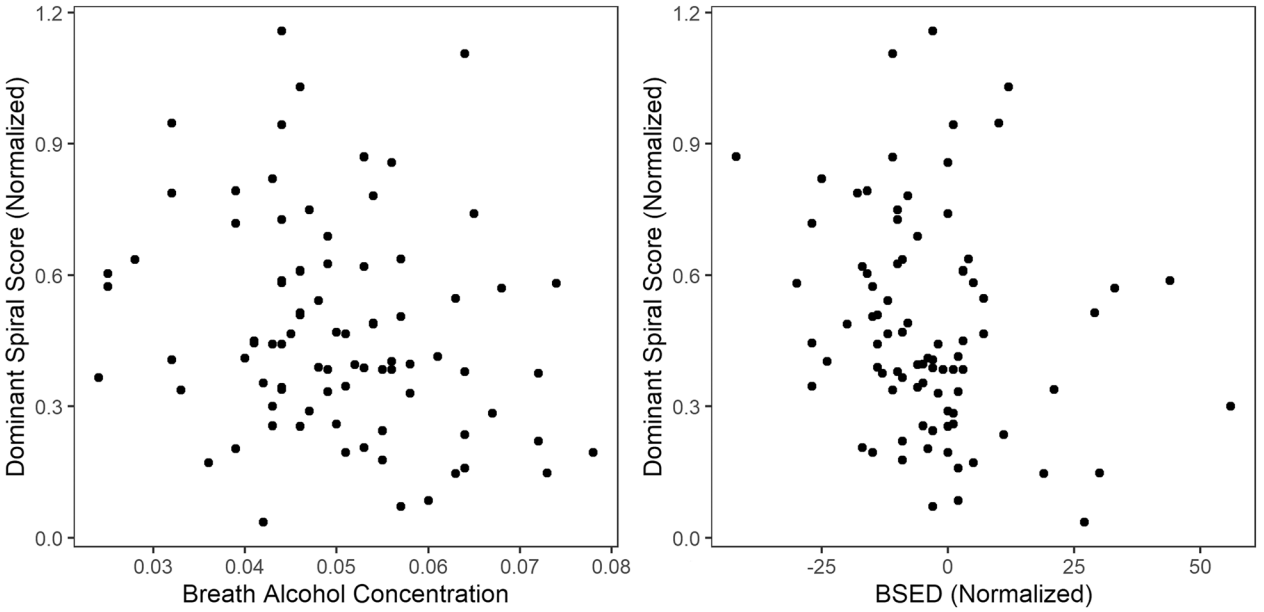

Figure 5. Scatterplot depicting the normalized dominant-hand spiral score for responders and the breath alcohol concentration (BrAC, left) and Sedation scores from the Biphasic Alcohol Effects Scale (BSED, right).

prespecified threshold definitions for tremor response, and the outcome measure selected with different levels of sensitivity (objective measure of tremor severity using digital spiral analysis in this study vs. visually rated Archimedes spirals in Hopfner et al.). It is important to recognize the responder rate depends very much on the definition, and our responder rate would be even higher if we did not constrain to a predefined timepoint.

We demonstrated that tremor improvement is not correlated with the nonmotor effects of ethanol, including stimulation and sedation. We did report a significant change in BSED (sedation) and a correlation between spiral score and BSED. The direction of change in the BSED indicated, however, that patients reported a reduction in sedation scores, which could be explained with ethanol's stimulatory effect at low levels. However, no significant correlation with increased stimulation was found (BSTIM). The data therefore suggest that the reduction in tremor after the ethanol is not driven by a sedative effect of ethanol.

These findings align with previous work demonstrating a specific CNS effect of ethanol in reducing tremor severity, as the effect on tremor in our sample of patients with ET appeared independent from the nonmotor effects of ethanol. These findings are also in line with prior work demonstrating ethanol's effect on the central tremor component in ET, while benzodiazepines, whose effect is via augmenting GABA, did not affect the central oscillator in ET.[30] While sedation is known to reduce overall tremor severity, our data further support the specificity of ethanol's effect, which is distinct from an indirect effect via sedation. As sedation may be largely a GABAergic effect, our data further speak against the theory of ethanol's effect in ET via benzodiazepine sensitive GABA receptors. Importantly, delta-subunit containing GABA receptors including the alpha6delta GABA receptors, which are expressed in cerebellar granule cells, are nonsensitive to benzodiazepines and have been shown to be sensitive to ethanol. These cerebellar GABA-A receptors therefore may facilitate the effect of ethanol in ET[41] and have been identified as potential targets for treatment development in ET.[24]

Lastly, we highlight a few limitations in our study. First, there was no blinding in the study, and thus, we cannot rule out the effects of bias or placebo effect. Second, while we used specific calculations for our patients to reach a BrAC level of 0.05 g/dL, there was variability in our data due to individual pharmacokinetic factors that could have contributed to our findings. Future studies involving IV-infusion of ethanol and utilizing a pharmacokinetic model-based algorithm to maintain a consistent BrAC level could help to eliminate this variability.

Third, although we used peer-reviewed and approved scales for assessing nonmotor symptoms in patients, these scales are imperfect and rely upon patient self-report. We cannot eliminate the possibility of questionnaire fatigue or confusion within our patients, which could have led to imprecise reports. Other environmental or personal factors could have also affected the responses of our participants, including pre-existing stress or mood. Future studies involving physiological measurements of stimulation and sedation could help to improve these factors. Future studies should furthermore assess the effect on effect in other action tremors, including ET-Plus, dystonic tremor, and PD tremor, to understand the specificity of this phenomenon.

One final limitation is that not all patients with ET drink alcohol. Therefore, while we demonstrate that ethanol was associated with a reduction in tremor severity in 80% of our patients, we note that this proportion and our related conclusions apply only to patients who drink alcohol. The percentage of alcohol responsiveness may be different when considering both those who report drinking alcohol and those who do not.

In conclusion, based on the data presented in the study, we postulate that tremor responsivity to ethanol is an inherent characteristic in ET and follows an exposure-response relationship. Furthermore, our data suggest that ethanol has a specific effect on tremor severity in patients with ET that appears to be independent of nonmotor effects. In particular, the effect on tremor reduction is not driven by greater sedation. Ethanol often improves tremor severity more than first-line pharmacotherapy, such as beta-blockers, anti-epileptics, or benzodiazepines. These findings provide valuable insight into possible mechanisms for this effect and future research into designing better treatment for ET.

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Author contributions

Patrick McGurrin, Gina Norato: Acquisition and analysis of data; drafting a significant portion of the manuscript or figures. **Johanna Thompson-Westra, Gayle McCrossin, Emily Lines, Sanjay Pandey**: Conception and design of the study; acquisition and analysis of data. **Codrin Lungu, Sule Tinaz, Bernhard Voller, Vijay Ramchandani, Mark Hallett and Dietrich Haubenberger**: Conception and design of the study; acquisition and analysis of data; drafting a significant portion of the manuscript or figures.

Conflict of interest

Dr. Haubenberger has been employed with the National Institutes of Neurological Disorders and Stroke, under which capacity this study was developed and conducted. Since January 2019, and after conclusion of this study, Dr. Haubenberger is a full-time employee of Neurocrine Biosciences, Inc. (San Diego CA). Dr. Haubenberger receives royalties from publishing from Oxford University Press. Dr. Voller was supported by the NINDS Intramural Program with supplemental funding from TG Therapeutics Inc. B. Voller and E. Lines were both sponsored by TG Therapeutics Inc. B. Voller worked as a contractor and as a special volunteer at the NIH/ NINDS in

accordance with the Cooperative Research and Development Agreement (CRADA 02036). E. Lines worked through the Postbaccalaureate Intramural Research Training Award Program at NIH/NINDS. Dr. Hallett is an inventor of a patent held by NIH for the H-coil for magnetic stimulation for which he receives license fee payments from the NIH (from Brainsway). He is on the Medical Advisory Boards of Brainsway, QuantalX, and VoxNeuro. He has consulted for Janssen Pharmaceuticals. He is on the Editorial Board of approximately 15 journals and receives royalties and/or honoraria from publishing from Cambridge University Press, Oxford University Press, Springer, Wiley, Wolters Kluwer, and Elsevier. Dr Lungu was an employee of the National Institutes of Neurological Disorders and Stroke during the contact of this study. Since August 2022, and after the conclusion of this study, Dr Lungu is a full-time employee of Pfizer, inc.

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